steroid hormone receptor..." It is clear from step (c) of original claim 1, that the recited method involves assessing the ability of a test compound to alter the binding of the labeled nucleic acid and/or the fluorescence-emitting compound to the steroid hormone receptor. The amended preamble better reflects that purpose.

Step a of claim 1 has been amended to recite "providing a solution comprising" the labeled nucleic acid, the fluorescence-emitting compound and the steroid hormone receptor. The order of adding and mixing these components is of no import and this amendment makes that clear.

Steps b and d of claim 1 has been amended to specify that fluorescence polarization measurements are taken of the labeled nucleic acid and the fluorescence-emitting compound that are present in the solutions of step a and step c at the excitation and emission wavelengths corresponding to each of them. This is identical in scope to the original language of step b, but makes clear what fluorescence polarization measurements are being taken and at what wavelengths that polarization is being measured.

Step c of claim 1 has been amended to recite "incubating the solution of step a) with at least one unlabeled compound that may affect the binding of said fluorescence-emitting compound or said fluorescence-labeled nucleic acid." The substitution of the term "unlabeled compound" for the term "molecule" is to avoid confusion with the recitation of "molecules" in the preamble (which is a reference to the fluorescent nucleic acid and the fluorescence-emitting molecule). Applicant has replaced the term "compete for interaction at least one domain" with "affect the binding of said fluorescence-emitting

compound or said fluorescence-labeled nucleic acid" to better specify what affect on binding the method is measuring. This amendment also is intended to include situations where the unlabeled compound added at step c causes unbinding of one or both of fluorescent molecules by a mechanism other than competition for binding. Such situations are clearly envisioned in applicants' originally filed application. See, for example, page 9, lines 16-19 (use of the method of the invention to detect molecules that interact with another part of the receptor, but affect the ability of a Fluormone to bind to the receptor's binding domain; use of the method to analyze the affect on DNA binding to a receptor domain of molecules binding to other domains); and Example 5, page 13, line 23 – page 14, line 10 (high KCl concentrations caused the labeled nucleic acid to be released from the estrogen receptor).

Step e of claim 1 has been amended to recite that comparison of fluorescence polarization measurements between steps b and d, "determine if said unlabeled compound affects the binding of said fluorescence-emitting compound or said fluorescence-labeled nucleic acid to the steroid hormone receptor." This amendment was necessitated by the Examiner's 35 U.S.C. §112, second paragraph rejection and is fully supported by the specification as filed.

Claim 4 has been amended to recite that the "difference in fluorescence polarization between the bound and unbound fluorescence-emitting compound and between the bound and unbound fluorescence-labeled nucleic acid is of sufficient magnitude to be suitable for use with a screening assay." The former recitation of "quantitation comparison of step e)" required amendment since the term "quantify any

interaction" has been deleted from claim 1. Moreover, the former language is meaningless if the fluorescence polarization values in steps b and d are identical because the compound added at step c had no effect on binding. The amended claim language better reflects applicants' intent that the difference in the fluorescence polarization values of bound versus unbound fluorescent molecules must be sufficiently high for the method to be useful in a screening assay (see, e.g., page 7, lines 18-19; and Figures 5 and 6).

The claims have also been amended to correct grammar and form. Claims 1, 2, 3 and 7 have been amended to recite the singular, rather than the plural form of "receptor." Claim 3 has been amended to recite that the purified hormone receptor "is a" recombinant receptor, rather than the former "comprises." Claim 7 has also been amended to insert the word "an" before "estrogen receptor."

Added claim 13 recites that the fluorescent labeled nucleic acid is a double-stranded DNA molecule. Support for this amendment is found in the specification at page 14, lines 6-7.

None of these amendments presents any new matter.

The Office Action

Applicants' cancellation of claims 9-12 is in response to the finality of the restriction requirement made December 6, 2001. The cancellation of these claims is without prejudice to applicants' ability to file for and obtain claims directed to the subject matter of claims 9-12 in applications claiming priority from the present application under 35 U.S.C. §120.

Claims 1-8 stand rejected under 35 U.S.C. §112, second paragraph, for being indefinite in the recitation of "any interaction" in step e of claim 1. Applicants traverse based upon the claim amendments presented herein. Applicants have deleted the term "any interaction" in step e of claim 1 and substituted therefor "determine if said unlabeled compound affects the binding of said fluorescence-emitting compound or said fluorescence-labeled nucleic acid to the steroid hormone receptor." The amended language complies with 35 U.S.C. §112, second paragraph and clarifies the specific intent of the method. Applicants request that the Examiner withdraw this rejection in light of this amendment.

Claims 1-8 stand rejected under 35 U.S.C. §103(a) as being "unpatentable" over Hwang et. al., Biochemistry, 31:11536-45, (1992) (Hwang) in view of U. S. Patent No. 5,445,935 ("the '935 patent"). Specifically, the Examiner contends that Hwang teaches fluorescent ligands for estrogen receptors and methods of measuring their binding to the estrogen receptor in the presence of potential competitors. According to the Examiner the '935 patent discloses a method of assaying the binding of fluorescently labeled estrogen response element DNA to the estrogen receptor by fluorescence polarization. The Examiner concludes that "[i]t would have been obvious ... to practice a method of measuring by fluorescence polarization the binding activities of molecules to steroid hormone receptors ... using fluorescent ligands and fluorescently labeled DNA." Applicants traverse.

Initially it should be pointed out that Hwang does not employ or suggest using fluorescence polarization to measure the association of the fluorescent ligand and the

estrogen receptor. Hwang's studies utilize fluorescence intensity (see, for Example, Figure 6, p. 11542). Thus, neither Hwang, nor the '935 patent teach or suggest using fluorescence polarization to determine if a fluorescent steroid-like molecule is bound to a steroid hormone receptor.

Moreover, as admitted by the Examiner, Hwang is not in any way directed to detecting the binding of a nucleic acid molecule to a steroid hormone receptor. Therefore, the method of Hwang cannot identify modulators of nucleic acid-steroid hormone receptor binding. Nor can Hwang's assay detect what effect, if any, a test compound that affects the binding of a fluorescence-emitting steroid-like compound to a steroid hormone receptor has on the ability that receptor to bind a nucleic acid.

The '935 patent is directed to the analysis of nucleic acid-steroid hormone receptor binding by fluorescence polarization. That patent makes no mention of and is not concerned with the binding at any other sites on a steroid hormone receptor other than the nucleic acid binding site. Accordingly, the methods taught in the '935 patent cannot identify modulators of steroid hormone-steroid hormone receptor binding, nor can they determine whether a test compound that affects the binding of a fluorescently labeled nucleic acid to a steroid hormone receptor has any affect on the binding of a fluorescently labeled steroid to another site on that same receptor.

There is no suggestion in either Hwang, or the'935 patent, to modify their methods so as to bind both a fluorescently labeled nucleic acid and fluorescence-emitting steroid-like compound to a steroid hormone receptor as is done in applicants' claimed methods. And there is no suggestion in either document to use such a complex to study

the affect of a test compound on the binding of each fluorescent molecule by fluorescence polarization, which is the basis of applicants' claimed invention. "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." In re Laskowski, 871 F.2d 115, 117, 10 U.S.P.Q.2d 1397, 1399 (Fed. Cir. 1989) (quoting In re Gordon, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984)). Accordingly, there is a lack of the requisite motivation to combine these two references. That lack of motivation renders the Examiner's obviousness rejection improper because "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." In re Napier 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995).

The Examiner asserts that the motivation to combine these two references is found in the '935 patent's teaching that "the disclosed assay methods may be used to test quantitatively the effects of specific ligands or other drugs on formation of complexes between proteins an[d] nucleic acids." Taken in the best light this statement suggests that the '935 patent method can evaluate the effect of a steroid hormone receptor ligand on the ability of a steroid hormone receptor to bind a nucleic acid – a site separate and distinct from the site where the ligand binds. There is however, no teaching or suggestion that the method of the '935 patent can or should be modified to evaluate the actual binding of a steroid hormone receptor ligand to the receptor – something applicants methods achieve. This is where the Examiner's assertion of motivation to

combine references fails. And this is where applicants' invention represents a patentable leap above and beyond the '935 patent or Hwang.

It is only in hindsight and with the present application in hand, that the Examiner can suggest that such a combination of documents be made. As set forth by the Federal Circuit in Grain Processing Corp. v. American Maize-Products Co., 840 F.2d 902, 5 U.S.P.Q.2D (BNA) 1788 (1988), such analysis is impermissible:

> "Care must be taken to avoid hindsight reconstruction by using "the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit." Orthopedic Equip. Co. v. United States, 702 F.2d 1005, 1012, 217 USPQ 193, 199 (Fed. Cir. 1983).

Id at 907.

Even if a suggestion or motivation to combine the '935 patent and Hwang exited (which it does not), such a combination would still fall short of rendering applicants' invention obvious. This is because Hwang does not utilize fluorescence polarization to evaluate the binding of a fluorescence-emitting ligand to a steroid hormone receptor. And neither Hwang, nor the '935 patent suggest using fluorescence polarization for that particular evaluation.

Prior to the present invention, it was unknown that the fluorescence-emitting compounds disclosed in Hwang would possess biochemical properties that would be suitable for use in fluorescence polarization. These properties include a sufficiently long lifetime, sufficiently tight binding affinity, stability at room temperature, low non-specific binding, and low interaction with solvents used in applicants' assays. All in all,

it would not have been obvious that those fluorescence-emitting compounds could even be used in fluorescence polarization.

In light of the above, it should be apparent that applicants invention, with its novel and unobvious use of two different fluorescent molecules to bind to two distinct sites on a steroid hormone receptor and to evaluate the affect of test compounds on either of such binding in a single assay, is patentable over the cited combination of Hwang and the '935 patent or any other combination of documents of which applicants are aware.

Accordingly, applicants request that the Examiner enter the amendments presented herein, consider the foregoing remarks and allow claims 1-8 and 13 to pass to issue.

Respectfully submitted,

Andrew S. Marks (Reg. No. 33,259)
Attorney for Applicants
Vertex Pharmaceuticals Incorporated
130 Waverly Street
Cambridge, MA 02139
Tel: (617) 444-6692
Fax: (617) 444-6483